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(54) Release Device for the Release of a Composition that Reacts to Heat

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(71) Applicant: Alza Corporation of Palo Alto, California, United States of America

(74) Agents: G.F. van der Beek et al.  
NEDERLANDSCH OCTROOIBUREAU  
Joh. de Wittlaan 15  
2517 JR The Hague

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The documents that are attached to this sheet are a copy of the originally filed description together with claim(s) and, if applicable, drawing(s).

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## RELEASE DEVICE FOR THE RELEASE OF A COMPOSITION THAT REACTS TO HEAT

This invention pertains to a release device that is both novel and useful. More particularly, the invention pertains to an osmotic release device for the release of a composition, which reacts to heat, with a beneficial agent therein, whereby this release takes place to usage surroundings at a controlled speed over the course of time.

Release devices for the release of a beneficial agent to usage surroundings are known technically. For example, US patent specification 3,760,984 (Theeuwes) discloses a release device that comprises a holder, which is capable of being shrunk by means of heat, and that is provided on the outside with an osmotic solute and a layer that is separated therefrom that comprises a polymer that is permeable to liquids. The release device is provided with a plug in order to fill the holder. The operation of the release device is based on the ability of a liquid to be imbibed into the device, whereby this liquid dissolves the solute and, as a result, a solution is formed that exerts pressure on the shrinkable holder and, as a result, it shrinks and releases the agent from the device. US patent specification 3,865,108 (Hartop) discloses a release device that comprises a compressible inner tube that contains a medicinal drug in a basic component that is formed from a swellable material. The device releases the medicinal drug as a result of the fact that the base and the components take up liquid from the surroundings and exert pressure on the compressible tube as a result of which the medicinal drug is driven out of the tube. Wichterle discloses a release device in US patent specification 3,971,376, whereby this release device comprises a capsule with walls that are made from one piece of material that is formed from a crosslinked gel that is capable of swelling in liquids. A textile fabric is incorporated in the material and provides strength and reduces problems that can arise as a consequence of the poor mechanical properties of the material when liquid is taken up at the time of operating the release device. Eckenhoff et al. disclose an improvement of an osmotic release device in US patent specification 3,987,790, whereby this release device comprises a line for filling a small pouch in the device. The device operates as a result of the fact that an osmotically active solute imbibes liquid into the device, and this liquid exerts hydraulic pressure on the pouch as a result of which it is compressed and the agent is squeezed out of the release device. US patent specification 3,995,631 (Higuchi et al.) describes a small pouch that is provided on the outside with a layer of an osmotic solute and a wall that is separated therefrom and that is formed from a material with a controlled permeability with respect to liquids. When the device is in use, a solution of the solute is formed that exerts pressure on the pouch; as a result of this, the agent is released from the pouch. Eckenhoff et al. disclose a release device in US patent specification 4,320,758, whereby this release device comprises a small flexible pouch, a casing comprising a dispersion of an osmotically active solute in a soluble polymer, and an outer wall that is permeable to liquids. The device releases a medicinal drug as a result of the fact that the casing imbibes water into the space between the outer wall and the pouch and thereby exerts hydraulic pressure on the pouch; as a result of this, the pouch is compressed and the medicinal drug is released from it.

The above mentioned release devices are usable for the release of a number of agents to usage surroundings, and these devices represent a commercial advance in dosing technology; however, it will be clear to someone who is skilled in the art that cases exist in which a release device, which has been made with a novel and inventive improvement, can be used and applied both generally and commercially in dosing technology. If, for example, a release device were made without a flexible pouch and without a woven component - whereby this signifies an improvement as a result of the fact that the number of steps and components that are needed for the manufacture of the release device are reduced - then such a device would gain acceptance immediately, and would represent an important improvement technically. If a release device were offered that does not have the limitation of the release devices in accordance with the prior art - namely that only dissolved or suspended agents are released - and that can now release agents that are soluble or insoluble in liquid or solid or similar forms, then such a release device would also be appreciated, and would likewise make a valuable contribution to the sectors comprising science, medicine, and commerce.

Thus an immediate objective of the invention is to provide a novel release device for the release of beneficial agents in all forms to usage surroundings, whereby this signifies an improvement in dosing technology.

Another objective of the invention is to provide a release device that is independent, self-starting, and self-driving in liquid surroundings, and that is easy to manufacture, and that can be used for the release of beneficial agents to animals, including humans, and to other biological and non-biological usage surroundings.

A subsequent objective of the invention is to provide a release device that can contain a hydrophobic composition, which reacts to heat and which has insoluble or soluble medicinal drugs therein, whereby this composition, which reacts to heat, undergoes a change in form as a consequence of the temperature of the biological surroundings, and becomes liquid, semi-solid, etc., and thereby accelerates the process of release from the device.

Yet another objective of the invention is to provide a release device that comprises a compartment, which contains a temperature-sensitive composition, and an expander component, which partially encloses the composition, and a semi-permeable outer wall, which encloses the component and the compartment, and a release passageway, whereby the release device releases the composition as a result of the combined physico-chemical effects of the composition's melting and becoming liquid, semi-solid etc., whereby the composition maintains an immiscible interface with the expandable component, and the expandable component swells and thereby expels a corresponding quantity of the composition from the device.

Yet a further objective of the invention is to provide a release device that is empty until it is filled with a solid composition, which becomes liquid at an elevated temperature, whereby, in the filled state, it can administer the composition, which becomes liquid, as a complete pharmaceutical course of treatment over a certain period of time, whereby intervention is necessary only at the beginning and end of the course of treatment.

Another objective of the invention is to provide a release device that can release beneficial agents that are taken up in a lipophilic, pharmaceutically acceptable vehicle, which reacts to heat and which melts in the presence of thermal energy to give a harmless composition that is capable of being administered, whereby irritation of mammalian tissue and interaction with mammalian protein tissue are avoided to a significant extent.

A subsequent objective of the invention is to provide an osmotic release device that comprises a eutectic composition, which is formed from at least two components and at least one medicinal drug, whereby this composition has a melting point at approximately the temperature of a warm-blooded animal and which, at that temperature, is released to the animal from the device.

Yet another objective of the invention is to provide a release device that can contain a hydrophilic composition, which reacts to heat and which contains medicinal drugs that range from insoluble through to soluble, whereby the composition that reacts to heat changes form and becomes capable of being administered as a consequence of the supply of energy from biological surroundings.

A subsequent objective of the invention is to provide a release device that contains a beneficial agent that is chemically unstable in aqueous surroundings and that can be taken up in a non-aqueous vehicle in the release device and that is shielded in the non-aqueous vehicle at the time of release from the device.

Other objectives, characterizing features, and advantages of the invention will become clear from the description, drawings, and claims that follow.

#### BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not to scale but which serve to illustrate the different forms of embodiment of the invention, the various figures have the following significance.

Fig. 1 is a view of a release device that has been designed and manufactured for orally administering a beneficial agent to a warm-blooded animal.

Fig. 2 is a cross section of the release device of Fig. 1 along the line 2-2, in which the internal compartment and the thermodynamic components are illustrated, whereby these form the device that is manufactured as an integral release device.

Fig. 3 is a cross section of the device of Fig. 1 in which the compartment is filled with a temperature-sensitive composition with a beneficial agent therein.

Fig. 4 is a cross section of the opened device of Fig. 3 in which the expansion of the propulsive component is illustrated that is used for the release of a beneficial agent from the device.

Fig. 5 is a cross section of Fig. 1 in which a closure component in the compartment is illustrated.

Fig. 6 illustrates a form of embodiment of the invention in which the components of the device are set up concentrically.

Fig. 7 illustrates a form of embodiment of the invention in which the components of the device are set up in a subdivided circular manner.

Fig. 8 illustrates a form of embodiment of the invention in which the components of the device are set up in a layered manner.

Fig. 9 illustrates a form of embodiment of the invention in which the components of the device are set up in the form of a pouch.

Fig. 10 is a flow diagram for three processes for the manufacture of the release device that is provided by the invention.

Fig. 11 is a graph that illustrates the speed of release from a release device.

Fig. 12 is a graph that illustrates the total quantity of the composition that is released from the device.

In the figures and in the description, identical components in related figures have been indicated by identical numbers. The concepts and forms of embodiments thereof, which occur earlier in the description of their implementation and in the description of the drawings, are explained elsewhere in the description.

#### COMPREHENSIVE DESCRIPTION OF THE DRAWINGS

The drawings are examples of novel and useful release devices for the release of a beneficial agent, and they are not to be construed as being limitative.

In Fig. 1, the release device 10 can be seen with a body 11, a wall 12, and a passageway 13 in the wall 12, whereby this passageway connects the interior of the device to the surroundings.

Fig. 2 is a cross section of the release device of Fig. 1 in which the device 10 comprises a body 11, a wall 12 around an internal compartment 14, and a passageway 13 in the wall 12, whereby this passageway connects the compartment 14 to the exterior of the device 10. The wall 12 is formed from a semi-permeable polymeric wall-forming composition, which is permeable to an external liquid but which is essentially impermeable to a beneficial agent and to other ingredients that are present in the compartment 14. The wall 12 is non-toxic and maintains its physical and chemical integrity throughout the life span of the release device 10.

Compartment 14 also contains a layer 15 of an expandable propulsive component that abuts the inside of the wall 12. The inner layer 15 partially encloses the compartment 14 except for an opening area 16 that is defined by the separated ends 17 of the layer 15. The inner layer 15 has a shape that corresponds to the shape of the semi-permeable wall 12 and the compartment 14. The layer 15 is manufactured from a hydrogel composition, which is either crosslinked or not crosslinked, and possesses osmotic properties such as the ability to imbibe an external liquid through the semi-permeable wall 12 and to exhibit an osmotic pressure gradient, over the semi-permeable wall 12, relative to a liquid outside the device 10.

Fig. 3 illustrates the device 10 of Fig. 1 in the form of a cross section. In Fig. 3, the device 10 comprises the same structural components as in Figs. 1 and 2, and, in the compartment 14, it also contains a beneficial agent 18, which is indicated by dots, and a heat-sensitive composition 19 that is indicated by wavy lines and that reacts to heat. The composition 19 is a release agent and a vehicle for the beneficial agent 18. The beneficial agent 18, which is located in compartment 14 and which can be released by the device, comprises agents that range from being insoluble through to being readily soluble in an aqueous liquid and a lipophilic medium. In a form of embodiment that is currently preferred, the composition 19, which reacts to heat, together with the agent 18 dispersed or dissolved homogeneously or heterogeneously therein, is formed from an anhydrous, heat-sensitive, hydrophilic or hydrophobic material that has approximately the properties of a solid substance at a temperature of 21°C or thereabouts, and has a melting point in the region of the body temperature of mammals of 37°C or thereabouts. In the invention, the terms "melting point", "softening point" or "[point of] becoming liquid" are used to indicate the temperature at which the composition, which reacts to heat, melts, goes into solution, or flows freely to give a vehicle that is capable of being administered, so that it can serve for releasing the agent 18 or 19.

When the release device 10 is in usage surroundings with a temperature of approximately 37°C, it releases the agent 18 via a combination of thermodynamic and kinetic effects. The heat-sensitive composition 19 then melts and forms a liquid-like, semi-solid, or similar phase that is capable of being delivered in order to release the agent 18 through the passageway 13. When the composition 19 melts, liquid is imbibed through the semi-permeable wall 12 by the hydrophilic layer 15 as a result of the tendency to achieve osmotic equilibrium; as a result of this, the layer 15 gradually swells and takes up more space in the compartment 14 while a non-mixing boundary is maintained at the interface. At the same time, the layer 15 pushes against the composition 19. As a result of the simultaneous expansion of the layer 15 and the contraction of the compartment 14 and the melting of the composition 19, the composition 19 with the agent 18 therein is released through the passageway 13 to the outside of the device 10. Figs. 3 and 4 together illustrate the operation of the device 10 for the release of the agent 18. In Fig. 3, the device 10 is illustrated at the beginning of the release procedure, and at the end of the release procedure in Fig. 4. The melting of the composition 19, and the immiscibility of the composition 19 and the expansion layer 15, and the swelling of the layer 15,

as can be seen in Fig. 4, with the associated volume reduction of compartment 14, as can be seen in Fig. 4, ensure that the agent 18 is released gradually and at a controlled speed.

Fig. 5 is a form of embodiment of the release device 10 of Figs. 1-4 in which a closure device 20 is also illustrated. The closure device 20 fits precisely into the compartment 14, and abuts the inner wall of the layer 15. The outside of the closure device 20 forms a liquid-proof sealing arrangement with the abutting portion of the inner surface of the layer 15. The closure device 20, which can be termed a plug, has a central hole 21 throughout its entire thickness. The hole 21 provides access to the interior of the device 10, and primarily to compartment 14, as a result of which the compartment 14 can be filled with the composition 19 with the beneficial agent 18 therein. At the same time, the hole 21 offers access to the passageway 13 in the semi-permeable wall 12 for the release, from the device 10, of the composition 19 with the beneficial agent 18 therein.

Figs. 6 and 7 illustrate other forms of embodiment of the release device 10 in accordance with the invention. The release device 10 of Figs. 6 and 7 is manufactured in accordance with a currently preferred process by co-extruding the structural components of the device 10. In Fig. 6, the device 10 is illustrated with the extremities 22 and 23 in the opened state, so that the structure of the device 10 can be seen. The device 10 essentially comprises a semi-permeable wall 24 that completely encloses the device (and hence also the extremities 22 and 23), and the expandable propulsive component 25, which is located in the middle, and a space 26 that is located inside it for the agent that reacts to heat. The device 10 also comprises a set of release openings 27 in the closed ends 22 and 23 of the semi-permeable wall 24 for the release of the composition with the beneficial agent, whereby these closed ends cannot be seen in the figure. Fig. 7 illustrates a device 10 that comprises a semi-permeable wall 28 that forms and delineates the outside of the device 10 and is cut through transversely at the ends 29 and 30 in the drawing, so that one can see the internal reservoir 31 for the agent, which reacts to heat, and a layer of a swellable propulsive component 32, whereby this layer abuts the agent that reacts to heat. Here, the device 10 has three release openings 33 through the semi-permeable wall 28 through which the beneficial agent can be released from the reservoir 31. One opening is located in the body of the device 10, and the other two are located at the closed extremities of the device. The device 10 of Figs. 6 and 7 operates as described above in usage surroundings.

Fig. 8 illustrates a rectangular embodiment of the device 10; however, the release device 10 can also have other shapes that are adapted to usage in certain liquid surroundings. In Fig. 8, the device 10 has been opened up along two of the lateral edges for the purpose of illustrating its internal structure. The device 10 comprises a release opening 35, a semi-permeable wall 36, a compartment 37 with a composition 38 that reacts to heat with a beneficial agent 39 therein, and a swellable propulsive agent 40. The device 10 serves for the release of the agent 39 as described above, i.e. the composition 38 that reacts to heat melts in the temperature range from 35 to 41°C, and the

composition 40, which abuts it in a layer-wise manner, then swells and forces the composition 39 through the opening 35.

Fig. 9 illustrates a release device 10 that can be manufactured in different sizes for use as a metering pump. In the form of embodiment that is illustrated, the device 10 has been miniaturized for use as an implant release device for administering a beneficial agent to an animal. The device 10 is illustrated in cross sectional form, and comprises a wall 41 of invariable shape that comprises, at least in part, a semi-permeable material surrounding an inwardly located swellable pouch-shaped component 42. The pouch 42 is an opened holder with an inner space 43 and an opening 50 that is closed by the closure device 44. The closure device 44 has a hole 45 that serves for filling and releasing. The pouch 42 contains a beneficial agent 44 and a vehicle composition 47 that reacts to heat. The passageway 49 in the semi-permeable wall 41 is located in the extension of the hole 45 for filling the device 10 and for releasing the beneficial agent 46 from the device.

Figs. 1-9 illustrate only a small number of the great variety of shapes, dimensions, and embodiments of devices for the release of beneficial agents to usage surroundings. The release device can be made for e.g. oral use with dimensions of 5 to 25 mm, or for use as an implant, an artificial gland, a device for implantation in the neck, womb, ear, nose, skin, vagina, rectum, rumen or first stomach of cattle, and as a subcutaneous release device. The release device can also be adapted for the release of an active agent in streams, in aquaria, on fields, in factories, in reservoirs, in laboratory equipment, in green houses, in transportation devices, in hospitals, in the ship building industry, for military objectives, in veterinary clinics, in nursing homes, on farms, in zoos, in chemical reactors, etc.

#### COMPREHENSIVE DESCRIPTION OF THE INVENTION

Surprisingly, it has now been found that the release device 10 can be provided with a wall comprising a semi-permeable material that does not have a disadvantageous effect on the host or an animal, and is permeable to an external aqueous liquid, such as water and biological liquids, and thereby remains essentially impermeable to agents such as medicinal drugs and osmotic agents, and it maintains its integrity in the presence of a thermotropic composition. The selective semi-permeable materials that form the outer wall are essentially insoluble in liquids, and they are essentially non-toxic and non-erodible.

Representative materials for forming the semi-permeable wall are, inter alia, semi-permeable homopolymers, semi-permeable copolymers, etc. In one form of embodiment, these materials are cellulose esters, cellulose monoesters, cellulose diesters, cellulose triesters, cellulose ethers, and cellulose ester ethers. These cellulose-like polymers have a degree of substitution (DS) at the anhydroglucose unit of more than 0 and ranging up to and including 3. The term degree of substitution is to be understood to mean the average number of hydroxyl groups that were originally

present in the anhydroglucose unit and that have been replaced by a substituting group or that have been converted into another group. The anhydroglucose unit can be either completely or partially substituted with groups such as acyl, alkanoyl, aroyl, alkyl, alkenyl, alkoxy, halogen, carboxyalkyl, alkyl carbamate, alkyl carbonate, alkyl sulfonate, alkyl sulfamate, and similar groups that form a semi-permeable polymer.

The following are included among the semi-permeable materials: cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose monoalkylates, cellulose dialkylates, cellulose trialkylates, cellulose monoalkenylates, cellulose dialkenylates, cellulose trialkenylates, cellulose monoaroylates, cellulose diaroylates, cellulose triaroylates, etc. Polymers that can serve as examples are, inter alia, the following: cellulose acetate with a DS of 1.8 to 2.3 and an acetyl content of 32 to 39.9%; cellulose diacetate with a DS of 1 to 2 and an acetyl content of 21 to 35%; cellulose triacetate with a DS of 2 to 3 and an acetyl content of 34 to 44.8%, etc. More specific cellulose polymers are, inter alia, the following: cellulose propionate with a DS of 1.8 and a propionyl content of 38.5%; cellulose acetate propionate with an acetyl content of 1.5 to 7% and a propionyl content of 39 to 42%; cellulose acetate propionate with an acetyl content of 2.5 to 3%, an average propionyl content of 39.2 to 45%, and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate with a DS of 1.8 and an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate with an acetyl content of 2 to 29.5%, a butyryl content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates with a DS of 2.9 to 3, such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trioctanoate, and cellulose tripropionate; cellulose diesters with a DS of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose propionate morpholinobutyrate, cellulose acetate butyrate, cellulose acetate phthalate, etc; mixed cellulose esters, such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptanoate, etc. Semi-permeable polymers are known from US patent specification 4,077,407 and can be made in accordance with the processes that are described in Encyclopedia of Polymer Science and Technology, part 3, pages 325-354, 1964, published by Interscience Publishers, Inc., New York.

Other semi-permeable polymers are, inter alia, the following: cellulose acetaldehyde dimethyl acetate [sic], cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose dimethylamino acetate; semi-permeable polyamides; semi-permeable polyurethanes, semi-permeable polysulfones [typo]; semi-permeable sulfonated polystyrenes; crosslinked selective semi-permeable polymers that are formed by co-precipitating a polyanion and a polycation as disclosed in US patent specifications 3,173,876, 3,276,586, 3,541,005, 3,541,006, and 3,546,142; selective semi-permeable silicone rubber compounds; semi-permeable polymers as disclosed by Loeb and Sourirajan in US patent specification 3,133,132; semi-permeable polystyrene derivatives; semi-permeable poly(sodium styrene sulfate); semi-permeable poly(vinyl benzyltrimethylammonium chloride); a semi-permeable

polymer with a permeability to liquids from  $10^{-1}$  to  $10^{-7}$  cm<sup>3</sup>.mil (25.4  $\mu$ m) per cm<sup>2</sup>, per hour, per atmosphere, expressed per atmosphere of hydrostatic or osmotic pressure difference over the semi-permeable wall. These polymers are known technically from US patent specifications 3,845,770, 3,916,899, and 4,160,020, and from the Handbook of Common Polymers, by Scott, J.R. and Roff, W.J., 1971, published by the CRC Press, Cleveland, Ohio.

The materials, which are used for forming the swellable inner wall and the small pouch, are polymeric materials as such and polymeric materials that have been mixed with osmotic agents that react to water or a biological liquid and that imbibe liquid and swell to give a state of equilibrium. The polymer has the ability to retain a considerable portion of the imbibed liquid in its polymeric molecular structure. In a form of embodiment that is currently preferred, the polymers are gel polymers that are capable of swelling to a very great extent, and they thereby generally undergo a 2-50 fold increase in volume. The swellable hydrophilic polymers with osmotic properties are also known as osmopolymers that can be either crosslinked or not crosslinked. The crosslinks can be covalent or ionogenic bonds, whereby the polymer has the ability to swell in the presence of a liquid, and - if it is not crosslinked - the polymer does not dissolve in an aqueous liquid. The polymers can be of vegetable, animal, or synthetic origin. Polymeric materials that are usable for the present objective are, inter alia, poly(hydroxyalkyl methacrylate) with a molecular weight from 5,000 to 5,000,000; polyvinylpyrrolidone with a molecular weight from 10,000 to 360,000; anionic and cationic expandable hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) with a low acetate residue; a swellable mixture of agar and carboxymethyl cellulose; a swellable composition comprising methyl cellulose mixed with very slightly crosslinked agar; a copolymer that is capable of swelling with water and that is made by dispersing a finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, or isobutylene; a polymer, which is capable of swelling with water, comprising N-vinylactams, etc.

Other polymers, which are capable of gelling and imbibing a liquid and retaining a liquid and which are usable for forming the hydrophilic expandable propulsive component are, inter alia, the following: pectin with a molecular weight ranging from 30,000 to 300,000; gelatine with a viscosity from 15 to 30 millipoise and a Bloom strength of 150 g; gelatine with a Bloom value of 160 to 250; polysaccharides such as agar, gum Arabic, karaya, tragacanth, algin, guar, and Carbopol<sup>(R)</sup> an acidic carboxy polymer and salt derivatives thereof; polyacrylamides; indene maleic anhydride polymers that are capable of swelling with water; Good-rite<sup>(R)</sup> a poly(acrylic acid) with a molecular weight from 80,000 to 200,000; Polyox<sup>(R)</sup> a poly(ethylene oxide) with a molecular weight from 100,000 to 5,000,000; starch graft copolymers; Aqua-keep<sup>(R)</sup> acrylate polymers with a water absorption capacity of 400 times their own weight; diesters of polyglucan [sic]; a mixture of crosslinked poly(vinyl alcohol) and polyvinylpyrrolidone; zein that is available as prolamine; poly(ethylene glycol) with a molecular weight from 4,000 to 100,000, etc. In a preferred form of embodiment, the expandable wall is formed from polymers and polymeric compositions that are capable of being molded thermally. Representative

polymers with hydrophilic properties are known from US patent specifications 3,865,108, 4,002,173, 4,207,893, and 4,327,725 and in the Handbook of Common Polymers, by Scott and Roff, published by the Cleveland Rubber Company, Cleveland, Ohio.

The osmotically active compound that can be mixed homogeneously or heterogeneously with the swellable polymer to give a propulsive wall is an osmotically active solute that is soluble in the liquid that is imbibed by the swellable polymer. These osmotically active compounds have an osmotic pressure gradient, over a semi-permeable wall, relative to an external liquid. Osmotically active compounds are also known as osmagents in dosing technology. Osmotically active osmagents, which are usable for this objective, are, inter alia, magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, mannitol, urea, sorbitol, inositol, sucrose, glucose, etc. The osmotic pressure in atmospheres (atm) of the osmagents that are suitable for the invention is greater than zero atm, and generally ranges from 8 to 500 atm or more.

The swellable expandable polymer ensures the propulsive force for the release of a beneficial agent from the release device, and it also serves as a supportive matrix for an osmotically active solute. The osmotic solute can be mixed homogeneously or heterogeneously with the polymer and, as a result, the desired swellable wall or swellable pouch is formed. In a currently preferred form of embodiment, the composition comprises at least one polymer and at least one osmotic solute. In general, a composition comprises approximately 20 to 90% by weight of polymer, and 80 to 10% by weight of osmotic solute with a preferred composition of 35 to 75% by weight of polymer, and 65 to 25% by weight of osmotic solute.

The term beneficial agent that is used here means a composition, preparation, or compound that can be released with the intention of achieving a pre-determined beneficial and useful result. The following are included among these: algicides, antioxidants, air-purifying agents, biocides, catalysts, chemical reactants, cosmetic agents, medicinal drugs, disinfectants, fungicides, foodstuffs, agents that inhibit fertility and agents that promote fertility, foodstuff additives, fermentation agents, germicides, insecticides, agents that weaken microorganisms, nutrients, agents that promote plant growth and agents that inhibit plant growth, preservatives, surface active substances, sterilizing agents, sterilizers of sexual fertility, vitamins, and other compositions that are useful for the surroundings or for the environment of animals. The agent can range from being insoluble to being readily soluble in the temperature-sensitive material that is taken up in the device.

In the specification and claims, the term medicinal drug is to be understood to mean any physiologically or pharmacologically active substance that has a local or systemic effect in animals including warm-blooded animals, humans and primates, and birds, fish, domesticated animals, animals used in sport, animals used for breeding, laboratory animals, and animals in zoos. The term physiological here relates to the administration of a medicinal drug that leads to normal concentrations

and functions. The term pharmacological relates here to variations in the reaction to the quantities of the medicinal drug that are administered to the host (see Stedman's Medical Dictionary, 1966, published by Williams and Wilkins, Baltimore). An active medicinal drug that can be released comprises inorganic and organic medicinal drugs without limitations, medicinal drugs that act on the nervous system, sedatives, sleep promoting preparations, stimulants, anticonvulsants, muscle relaxants, anti-Parkinson agents, analgesics, anti-inflammatory agents, antimalarial agents, hormonal agents, contraceptive agents, sympathicomimetic agents, diuretics, antiparasitic agents, hypoglycemic agents, ophthalmic drugs, electrolytes, diagnostic agents, and cardiovascular agents. The quantity that is present in the release device can vary from 0.05 ng to 20 g or more. For medical applications, the device can contain different quantities, e.g. 25 ng, 1 mg, 125 mg, 1.5 g, etc. of the agent. The device can be used one or more times per day, one or more times per week, etc.

The term "reacting to heat" that is used for the invention encompasses thermoplastic compositions that can become soft as a reaction to heat, and that can become hard again upon cooling. The term also encompasses thermotropic compositions that can undergo a change as a reaction to the gradual supply of energy. These materials are also temperature-sensitive in their reaction to the supply and removal of energy. The term "reacting to heat" as used in a preferred form of embodiment for this invention means the physico-chemical ability of a composition comprising the agent and vehicle to exhibit solid or solid-like properties at temperatures up to 34°C, usually between 20°C and 33°C, and to become liquid, semi-solid, or viscous starting from 33°C, or generally in the region from 33°C to 40°C, as a result of the supply of heat. The vehicle that reacts to heat is heat-sensitive and, at an elevated temperature, it has the ability to melt, dissolve, go into solution, become soft or become liquid, as a result of which the release device can release the vehicle, which reacts to heat, along with the beneficial agent that is homogeneously or heterogeneously mixed into it. The vehicle that reacts to heat can be lipophilic, hydrophilic, or hydrophobic. Another important property of the vehicle is its ability to maintain the stability of the agent, which is present therein, during storage and during the release of the agent. Representative compositions, which react to heat, and their melting points are as follows: cocoa butter: 32-34°C; cocoa butter plus 2% beeswax: 35-37°C; propylene glycol monostearate and propylene glycol distearate: 32-35°C; hydrogenated oils such as hydrogenated vegetable oil: 36-37.5°C; 80% hydrogenated vegetable oil and 20% sorbitan monopalmitate: 39-39.5°C; 80% hydrogenated vegetable oil and 20% polysorbate 60: 36-37°C; 77.5% hydrogenated vegetable oil, 20% sorbitan trioleate, and 2.5% beeswax: 35-36°C; 72.5% hydrogenated vegetable oil, 20% sorbitan trioleate, 2.5% beeswax, and 5.0% distilled water: 37-38°C; monoglycerides, diglycerides, and triglycerides of acids with 8-22 carbon atoms, including saturated and unsaturated acids such as palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and arachidonic acid, and the triglycerides of saturated fatty acids with monoglycerides and diglycerides: 34-35.5°C; monostearates and distearates of propylene glycol: 33-34°C; partially hydrogenated cotton seed oil: 35-39°C; hardened fatty alcohols and fats: 33-36°C; hexadienol and anhydrous lanoline triethanolamine glyceryl monostearate: 38°C; eutectic mixtures of monoglycerides, diglycerides, and

triglycerides: 35-39°C; Witepsol<sup>(R)</sup> # 15, a triglyceride of saturated vegetable fatty acids with monoglycerides: 33.5-35.5°C; Witepsol<sup>(R)</sup> H32 that is free from hydroxyl groups: 31-33°C; Witepsol<sup>(R)</sup> W25 with a saponification number of 225-240 and a melting point of 33.5-35.5°C; Witepsol<sup>(R)</sup> E 75 with a saponification number of 220-230 and a melting point of 37-39°C; a poly(alkylene glycol) such as poly(ethylene glycol) 1000, a non-branched polymer of ethylene oxide: 38-41°C; poly(ethylene glycol) 1500, melting point: 38-41°C; poly(ethylene glycol) monostearate: 39-42.5°C; 33% poly(ethylene glycol) 1500, 47% poly(ethylene glycol) 6000, and 20% distilled water: 39-41°C; 30% poly(ethylene glycol) 1500, 40% poly(ethylene glycol) 4000, and 30% poly(ethylene glycol) 400: 33-38°C; a mixture of monoglycerides, diglycerides, and triglycerides of saturated fatty acids with 11-17 carbon atoms: 33-35°C, etc. The composition that reacts to heat is an agent for storing a beneficial agent in a solid composition at a temperature of 20-33°C, for maintaining an immiscible boundary at the interface with the swelling composition, and for releasing the agent in a more or less liquid composition at a temperature that is higher than 33°C and usually 33-40°C. In the case of the release of compositions, which react to heat, in biological surroundings, these compositions are readily secreted, metabolized, assimilated, etc. in order that the beneficial agent can be used actively.

The semi-permeable wall can be installed on the expandable wall or pouch or on the layer, which reacts to heat, by molding, casting, spraying, or submerging using a composition that forms a semi-permeable wall.

Other processes that are currently preferred and that can be followed for the installation of the wall are the air suspension method and the "pan coating" method. The air suspension method comprises suspending the laminate or pouch in a stream of air and letting it whirl around together with a composition, which forms a semi-permeable wall, until the component is enclosed and coated by the wall. The process can be repeated with a different composition, which forms a semi-permeable wall, so that a semi-permeable layered wall is produced. The air suspension method is described in US patent specification 2,799,241, J. Am. Pharm. Assoc., part 48, pages 451-459, and ibid., part 49, pages 82-84, 1960. Other standard manufacturing procedures are described in Modern Plastics Encyclopedia, part 46, pages 62-70, 1969, and in Pharmaceutical Sciences, by Remington, 14th edition, pages 1626-1678, 1970, published by Mack Publishing Co., Easton, PA.

Solvents that are suitable for the manufacture of the walls are e.g. inert inorganic and organic solvents that do not damage the materials, or the composition, which reacts to heat, or the expandable wall, or the small pouch, or the final release device. The following are generally included in this group: water-based solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, alicyclic hydrocarbons, aromatic hydrocarbons, heterocyclic solvents, and mixtures thereof. Applicable solvents are, inter alia, the following: acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butanol, methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, methyl isobutyl ketone, methyl propyl ketone, hexane, heptane, ethylene glycol monoethyl

ether, ethylene glycol monoethyl acetate, dichloromethane, 1,2-dichloroethane, 1,2-dichloropropane, carbon tetrachloride, nitroethane, nitropropane, tetrachloroethane, diethyl ether, diisopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water, and mixtures of these such as acetone/water, acetone/methanol, acetone/ethanol, dichloromethane/methanol, and dichloroethane/methanol. In this invention, the semi-permeable wall is generally installed at temperatures that are several degrees below the melting point of the composition that reacts to heat. Instead of this, the thermoplastic composition can be installed in the release device after the semi-permeable wall has been installed.

The expandable wall, the pouch-like component, or the expandable layer can be manufactured in accordance with conventional thermo-forming polymer processes such as spraying a spindle, submerging a mold in a wall-forming composition, blow molding, vacuum forming, pressure molding, injection molding, extruding, and laminating. In a currently preferred form of embodiment, a pouch-like component or expandable molded propulsive component is manufactured in accordance with the pressure molding process that is illustrated in Fig. 10. Use is made of a casting cavity and a plunger in the case of pressure molding. The casting cavity (mold) forms a surface of the cast component, and the polymeric wall-forming composition is introduced into the mold. The plunger forms the other surface of the cast component. When the mold is closed, the plunger compresses the polymeric composition into the shape of the final pouch-like component. The mold and the plunger are held in this position until the polymeric composition has become hard. In Fig. 10, the pouch-like component or the cast propulsive component is indicated by the letter a and is illustrated after the pressure mold has been removed. In one form of embodiment, the small pouch is then brought to the filling point b where it is positioned under a filling funnel and filled with a molten composition with the agent therein. After cooling, the filled compartment is coated at c with a semi-permeable wall and an opening is bored through the semi-permeable wall using a laser, and this generates the release device. In a similar process, the shaped compartment a is closed at d by means of a closure device, which is provided with a filling and discharging hole, and the closed compartment is filled at room temperature at the filling point e with a molten composition. Finally, the filled compartment is coated at f with a semi-permeable wall, and a laser bores an opening through this wall in the extension of the hole, and the release device is thus obtained. In a similar process, the closed compartment is coated at g with a semi-permeable membrane, and a laser bores an opening through this wall in the extension of the hole, as a result of which the empty release device is produced. This is then filled at h at room temperature with the molten preparation, after which the final release device is produced.

The terms opening and passageway that are used here encompass provisions in the semi-permeable wall through which a preparation with a beneficial agent can be released from the release device. The opening can be formed by mechanical drilling, or by boring with a laser, or by eroding an erodible element in the wall such as a gelatine plug. A comprehensive description of openings and

the maximum and minimum dimensions that are preferably applicable to an opening are disclosed in US patent specifications 3,845,770 and 3,916,899.

### DESCRIPTION OF THE EXAMPLES

The following examples will illustrate the invention, but they should not be seen as limiting the usage possibilities of the invention.

#### Example I

A release device is manufactured as follows: an expandable capsule-shaped holder is formed by injection molding a polymer composition. The holder has a diameter of 12 mm and a depth of 40 mm. The wall of the holder is formed from a composition that comprises 30% by weight of sodium chloride and 70% by weight of poly(ethylene oxide) with a molecular weight of 3,000,000. The wall-forming components are mixed for 20 minutes in a commercially obtainable mixer to give a homogeneous composition. The composition is compressed to give tablets, and then it is introduced into an injection molding apparatus and the holder is formed by injection molding at 145-150°C at a pressure of 6.5-7.0 x 10<sup>5</sup> kPa.

The holder is then filled with a heat-sensitive composition that comprises 0.5% by weight of theophylline, 77% by weight of hydrogenated vegetable oil, 20% by weight of sorbitan trioleate, and 2.5% by weight of beeswax. The filling process takes place at 36-37°C. After cooling to 21°C, the semi-permeable outer wall is installed on the filled holder by coating in a Wurster air suspension coating apparatus. The semi-permeable wall is formed from a solution of 5% by weight of cellulose acetate butyrate in dichloromethane. The semi-permeable wall is installed in such a way that it has a thickness of 0.4 mm, and the filled and coated holder is dried for 5 to 10 days in an oven at 50°C. Finally, a laser is used to bore a 0.75 mm opening through the semi-permeable wall for the release of the medicinal drug preparation from the compartment of the release device.

#### Example II

A holder is made in accordance with Example I, and then it is filled with a medicinal drug preparation that comprises 0.20 g of paracetamol, 0.02 g of codeine phosphate, 0.15 g of acetylsalicylic acid and 2.0 g of Witepsol<sup>(R)</sup> H35, a mixture of glycerol esters of saturated fatty acids in which lauric acid predominates. The composition is prepared by finely grinding and thoroughly mixing all the components, and then adding the Witepsol vehicle at 38-40°C. The holders are filled with the molten composition that acquires a creamy consistency upon cooling. The holders are coated with a semi-permeable wall, and an opening is bored in them as above.

#### Example III

A release device with a compartment that contains a temperature-sensitive composition, which reacts to heat and which has been installed on an expandable composition, is manufactured as

follows. A mold is sequentially filled with a molten composition - which comprises 2.5% of phenobarbital, 20.5% of glyceryl-glycerine, 77.0% of theobromine oil, and a glyceride of stearic acid, palmitic acid, and lauric acid and which, upon cooling to room temperature, forms the layer that reacts to heat - and then with a mixture of 30 parts of ethylene glycol monomethacrylate, 0.12 parts of ethylene glycol dimethacrylate, and 10 parts of a 0.13% solution of sodium disulfate in water/ethanol. This mixture polymerizes at 30°C, and the solid laminate is removed from the mold 20 minutes after establishing equilibrium conditions at room temperature.

A 15% by weight solution of cellulose acetate with an acetyl content of 39.8% is then prepared in acetone, and the laminate is coated by submerging it 15 times in this solution, namely for 10 seconds first of all, and then for 1 minute for each immersion with drying for 5 minutes in between in each case. After submersion, the release devices are dried for 10 days at 22°C. A 0.7 mm semi-permeable wall, which regulates the speed of transit through it, is formed around the laminate as a result of this process. A passageway is bored through the semi-permeable wall using a laser, whereby this passageway connects the exterior of the device to the layer that reacts to heat.

#### Example IV

A release device is manufactured as follows. A heat-sensitive eutectic mixture comprising 77% of neutral fat with a melting point of 35-37°C and 19.5% of paraffin wax with a melting point of 52°C is heated until it is liquid. 3.5% of acetylsalicylic acid is added to the melt, and the mixture is cast in a mold. After cooling and solidification, 500 mg of Cyanamer<sup>(R)</sup> polyacrylamide, a hydrogel with a molecular weight of approximately 200,000, is introduced into the mold, and the layers are compressed to give a layer, which reacts to heat and which is in contact with a hydrogel layer, and the layers that abut each other are removed from the mold.

A semi-permeable wall is then installed by mixing 85 g of cellulose acetate with an acetyl content of 39.8% with 200 mL of dichloromethane, and 200 mL of methanol, and coating the component, which forms the two-layer compartment, by spraying in an air suspension apparatus until a 0.25 mm thick semi-permeable wall has formed around the compartment. The devices are dried for two weeks, and a laser is used for boring a 0.4 mm passageway through the semi-permeable wall, whereby this passageway forms the connection to the heat-sensitive composition.

#### Example V

The process in Example IV is repeated using the compositions that are described therein, except that, in this example, the composition, which reacts to heat, comprises a polyhydroxy compound that has been partially esterified with (C<sub>14</sub>-C<sub>18</sub>) fatty acids and that has been reacted with 2 to 5 epoxide units. The composition comprises a medicinal drug, and the composition, which reacts to heat, melts rapidly and completely at the temperature of the body to give a liquid composition that can be released with ease from the release device.

Example VI

The processes of Examples IV and V are repeated for the preparation of a composition, which reacts to heat and which comprises 85 mg of sorbitan monostearate that has been reacted with 4 epoxide units and that has a melting point of 5°C, together with 5 mg of sorbitan monostearate, which has been reacted with 20 epoxide units, 5 mg of sorbitan monoricinoleate and 15 mg of sodium indomethacin.

Example VII

A heat-sensitive composition for use in the release device of Example I is prepared by mixing, with the application of heat, 30% of poly(ethylene glycol) 1500, 30% of poly(ethylene glycol) 4000, 30% of poly(ethylene glycol) 400, 9% of cocoa butter and 1% of oxyprenolol hydrochloride. The composition has a melting time of 15 to 20 minutes at 37°C.

Example VIII

A composition, which mainly comprises 65% of sodium chloride, 20% of Polyox<sup>(R)</sup>, a polyoxyethylene with a molecular weight of approximately 200,000, and 15% of poly(ethylene glycol) 200,000, is introduced, by means of injection molding, into an osmotic capsule in the form of a thin-walled cylinder with a hemispherical bottom. The injection molding conditions were as follows:

temperature of the injection nozzle	$180 \pm 20^\circ\text{C}$
zone 1	off
zone 2	$230 \pm 25^\circ\text{C}$
zone 3	$220 \pm 25^\circ\text{C}$
temperature hot point	$180 \pm 25^\circ\text{C}$
temperature casting cavity	$18 \pm 3^\circ\text{C}$
temperature core pen	$8 \pm 3^\circ\text{C}$
temperature stopper plate	$8 \pm 3^\circ\text{C}$
lamp time	$13.5 \pm 2$ seconds
injection time	$1.9 \pm 0.5$ seconds
injection speed	$5 \pm 1$
injection pressure	$84 \pm 7 \text{ kg/cm}^2$
counter pressure	$42 \pm 7 \text{ kg/cm}^2$
cycle time	20 seconds

The internal and external diameters were 11.7 and 13.3 mm respectively, and the internal and external lengths were 37.0 and 38.5 mm respectively.

The osmotic capsule was filled with 2.88 g of H-15 Witepsol, a glycerol ester of a saturated fatty acid with 0.1% of red dye oil. The filled osmotic capsules were coated in a pan coater (Accela-Cota) with cellulose acetate butyrate in a solvent comprising 95% of dichloromethane and 5% of ethanol, until a semi-permeable membrane was formed with a uniform thickness of 0.5 mm. The devices were dried for 7 days at 55°C, and a 1 mm outlet was bored. The release speed of these devices was examined. Fig. 11 illustrates the speed of release of the heat-sensitive composition from the system in mg/hour per day. Fig. 12 illustrates the cumulative quantity of heat-sensitive composition that is released as a percentage of the total quantity that is delivered by the system. The circles relate to release from the device in the vertical position, and the squares relate to release from the device in the horizontal position.

One form of embodiment of the invention relates to a process for the administration, at a controlled speed, of a beneficial medicinal drug into the vaginal or rectal passage of a warm-blooded animal, whereby this process comprises the following steps: (A) a release device is introduced into the bodily passage, whereby this release device comprises the following components: (1) an inner wall that is formed from a swellable polymeric composition that forms and encloses an internal compartment; (2) a nozzle in the inner wall; (3) a preparation comprising a beneficial medicinal drug in the compartment, whereby this preparation comprises a unit quantity of a medicinal drug for implementing a therapeutic program, and a heat-sensitive vehicle, which melts or dissolves at the temperature of the body, together with an agent for the transportation of a medicinal drug out of the device; (4) an outer wall around the inner wall and the nozzle, whereby this outer wall is formed from a semi-permeable polymeric composition that allows liquid to pass through it, but it does not allow the medicinal drug to pass through it; and (5) an opening through the outer wall, whereby this opening forms a connection to the internal compartment via the nozzle; (B) liquid is imbibed through the inner wall via the semi-permeable wall at a speed that is determined by the permeability of the semi-permeable wall and the osmotic pressure gradient over the semi-permeable wall, as a result of which the inner wall swells; (C) the medicinal drug preparation in the compartment melts and becomes a liquid preparation; and (D) the preparation, together with the beneficial medicinal drug, is released from the compartment as a result of the fact that the inner wall swells and exerts pressure on the molten preparation, as a result of which the preparation is released in a therapeutically active quantity and at a controlled speed through the passageway and thus has the desired medical effect over an extended period of time, e.g. 1 hour up to several months, and preferably from 1 to 24 hours.

Although the preceding description comprises preferred forms of embodiments of the invention, it is to be noted that variations and adaptations, which are in conformity with the disclosed inventive principles, can be made without deviating from the tenor of the invention.

CLAIMS

1. Release device for the release, at a controlled speed, of a preparation comprising a beneficial agent to usage surroundings, whereby this preparation is sensitive to heat, with the following as characterizing features:

a) an inner wall that encloses and forms an internal compartment that contains the preparation comprising the beneficial agent, whereby this wall has an opening through which the preparation can be introduced into the compartment and from which the preparation can be released, whereby this wall is formed from a composition that is an agent that absorbs liquids and swells in the compartment;

b) an outer wall around the inner wall, whereby this outer wall is formed from a composition that is permeable to a liquid and essentially impermeable to a beneficial agent; and

c) a passageway in the outer wall, whereby this passageway provides a connection to the opening through which a preparation of a beneficial agent can be released from the device.

2. Release device in accordance with Claim 1, with the characterizing feature that the compartment contains a preparation comprising a beneficial agent that is solid up to 33°C and that melts above 33°C.

3. Release device in accordance with Claim 1 or 2, with the characterizing feature that the inner wall is formed from a composition that comprises a hydrogel polymer and an osmotically active solute.

4. Release device in accordance with Claim 1 or 2, with the characterizing feature that the inner wall is formed from a composition that comprises a hydrogel polymer that swells in the presence of liquid.

5. Release device in accordance with one of the Claims 1-4, with the characterizing feature that a closure device, which is provided with a hole, is located in the opening in the inner wall.

6. Release device in accordance with one of the Claims 1-5, with the characterizing feature that the outer wall is formed from a cellulose ester, a cellulose diester, a cellulose triester, a cellulose ether, or a cellulose ester ether, such as cellulose acetate, cellulose diacetate, cellulose triacetate, or cellulose acetate butyrate.

7. Release device in accordance with one of the Claims 1-5, with the characterizing feature that the outer wall is formed from a hydrophilic composition that swells in the presence of aqueous liquids that are imbibed into the device.

8. Release device in accordance with Claim 1 or 2, with the characterizing feature that the inner wall is formed from a poly(ethylene oxide).

9. Release device in accordance with Claim 1 or 2, with the characterizing feature that the inner wall is formed from a poly(ethylene oxide) and an osmotically active solute.

10. Release device in accordance with one of the Claims 1-9, with the characterizing feature that the compartment contains a composition that is sensitive to heat and that comprises a glycerol ester of a saturated fatty acid.

11. Release device for the release, at a controlled speed, of a beneficial agent to liquid biological usage surroundings with a temperature of more than 33°C, with the following as characterizing features:

- a) a wall that is formed from a semi-permeable polymeric composition around and delineating;
- b) a compartment;
- c) a first provision in the compartment, whereby this first provision changes from a solid composition to a spreadable composition as a reaction to the temperature of the biological surroundings, and whereby this first provision contains a beneficial agent and is installed on a second provision in the compartment, whereby this second provision imbibes liquid through the semi-permeable wall and swells in the compartment; and
- d) a passageway in the wall, whereby this passageway connects the outside of the device to the first provision.

12. Release device in accordance with Claim 11, with the characterizing feature that the first provision is a layer.

13. Release device in accordance with Claim 11 or 12, with the characterizing feature that the second provision is a layer.

14. Release device in accordance with one of the Claims 11-13, with the characterizing feature that the solid composition is a gel.

15. Release device in accordance with one of the Claims 11-14, with the characterizing feature that the solid composition melts as a reaction to the temperature of the biological surroundings.

16. Release device in accordance with one of the Claims 11-14, with the characterizing feature that the solid composition becomes liquid as a reaction to the temperature of the biological surroundings.

17. Release device for the release, at a controlled speed, of a beneficial agent to liquid surroundings at a temperature that corresponds to the temperature of a warm-blooded animal, with the following as characterizing features:

- a) a wall that is formed from a semi-permeable polymeric composition that delineates a closed tube with an internal compartment therein;
- b) a first provision that is positioned in the middle of the compartment and that changes from a non-spreadable composition to a spreadable composition as a reaction to the temperature of the surroundings and that contains a beneficial agent and that is enclosed by a second provision in the compartment, whereby this second provision imbibes liquid through the semi-permeable wall and swells up against the first provision; and
- d) [sic] a passageway in the wall, whereby this passageway connects the outside of the device to the first provision.

18. Release device in accordance with Claim 17, with the characterizing feature that the second provision is positioned between the first provision and the inside of the wall.

19. Release device in accordance with Claim 17 or 18, with the characterizing feature that the passageway is located in the wall, namely at the closed extremity of the tube.

20. Release device in accordance with one of the Claims 17-19, with the characterizing feature that the non-spreadable composition is a semi-solid substance.

21. Release device in accordance with one of the Claims 17-19, with the characterizing feature that the non-spreadable composition is a solid substance.

22. Release device in accordance with one of the Claims 17-19, with the characterizing feature that the non-spreadable composition does not flow at a temperature below 33°C.

23. Release device for a beneficial agent with the following as characterizing features:

- a) a tubular body that is closed at its extremities and that is formed from a polymeric composition that is permeable to an external liquid and that is essentially impermeable to a beneficial agent;
- b) a compartment in the body;
- c) a first layer in the compartment, whereby this first layer is formed from a composition that comprises a beneficial agent and a vehicle for the beneficial agent;
- d) a second layer in the compartment, whereby this second layer abuts the first layer and is formed from a hydrogel that swells in the presence of the liquid that is entering the compartment; and

e) a passageway in the body, whereby this passageway connects the outside of the device to the first layer.

24. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic, pharmaceutically acceptable hydrogenated oil.

25. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic monoglyceride, diglyceride, or triglyceride.

26. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic hydrophilic polymer with a molecular weight of more than 1,000.

27. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic eutectic composition that comprises a glyceride and a hydrogenated oil.

28. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic glyceride of a fatty acid with 8 to 12 carbon atoms.

29. Release device in accordance with Claim 23, with the characterizing feature that the vehicle is a non-toxic composition that comprises a mixture of at least two poly(ethylene glycols) of which one has a molecular weight in excess of 1,000.

30. Release device for the release, at a controlled speed, to usage surroundings of a heat-sensitive preparation with a beneficial agent, with the following as characterizing features:

a) an inner wall that encloses and forms an internal compartment that contains the preparation comprising the beneficial agent, whereby this wall has an opening through which the preparation can be introduced into the compartment and from which the preparation can be released, whereby this wall is formed from a composition that is an agent that absorbs liquids and swells in the compartment;

b) an outer wall around the inner wall, whereby this outer wall is formed from a composition that is permeable to a liquid, and that is essentially impermeable to a beneficial agent, and that is a composition that comprises a polysulfone, a polyacrylate, a polymethacrylate, or a polyurethane; and

c) a passageway in the outer wall that provides a connection to the opening through which a preparation comprising a beneficial agent can be released from the device.

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FIG.1

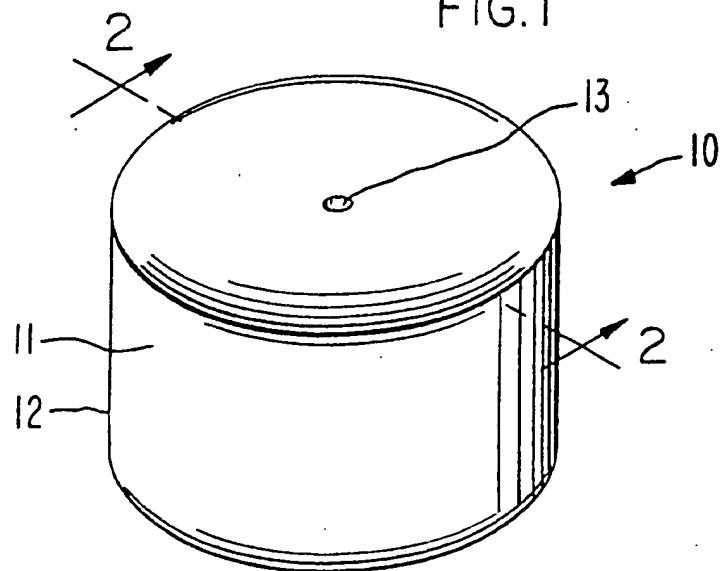


FIG.2

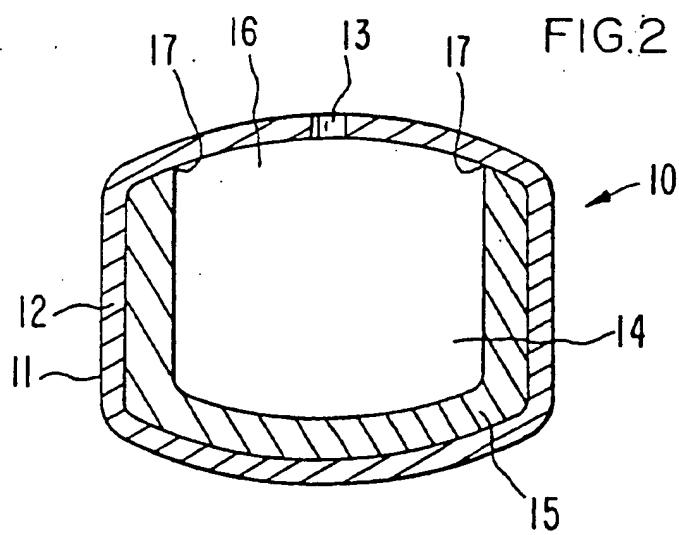
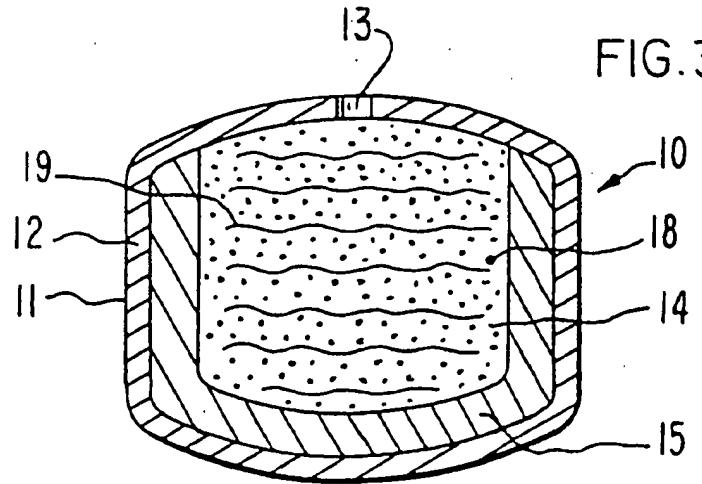


FIG.3



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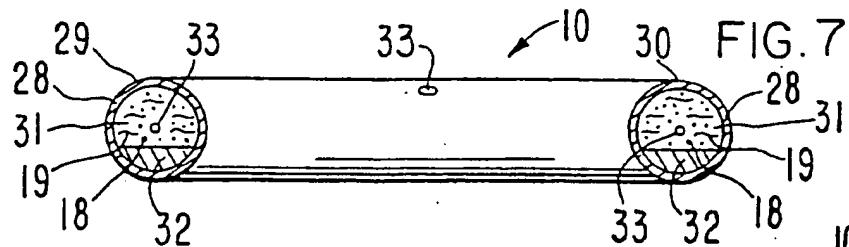
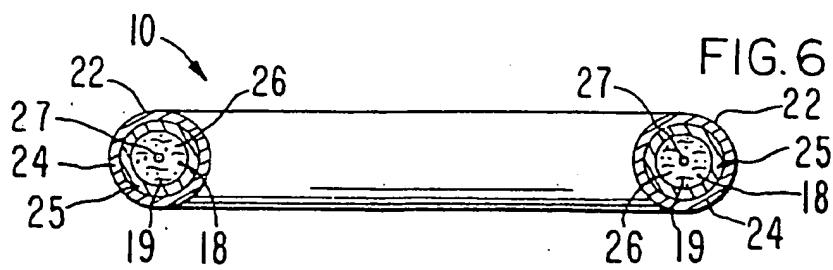
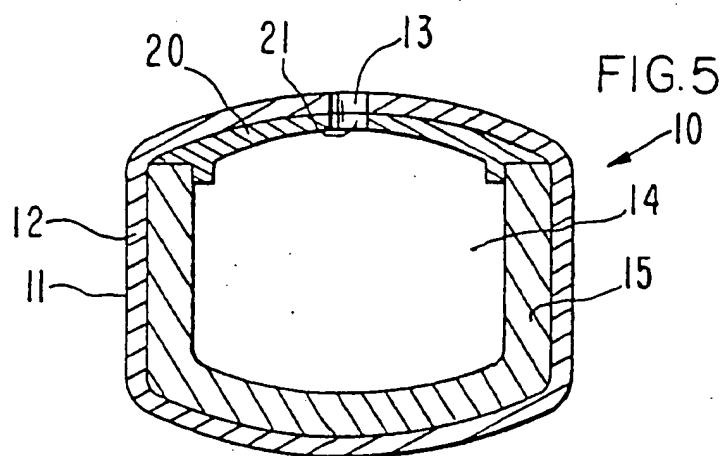
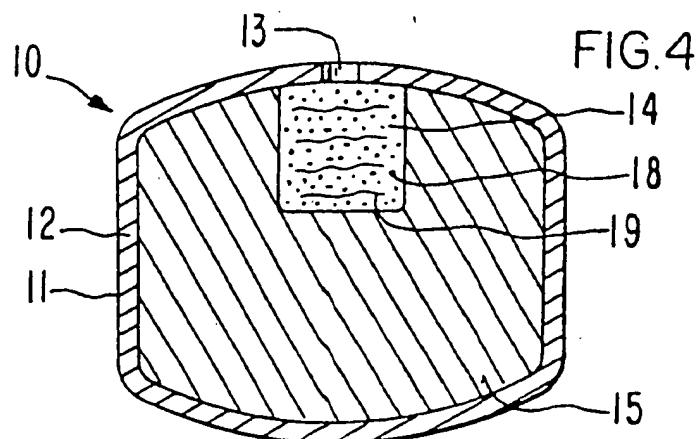
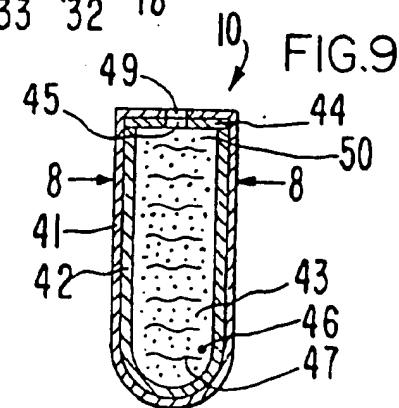
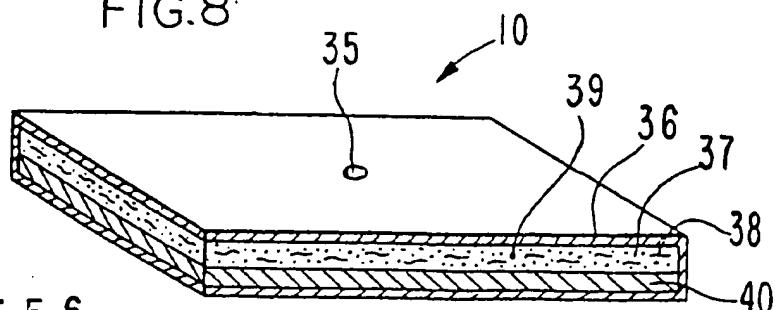
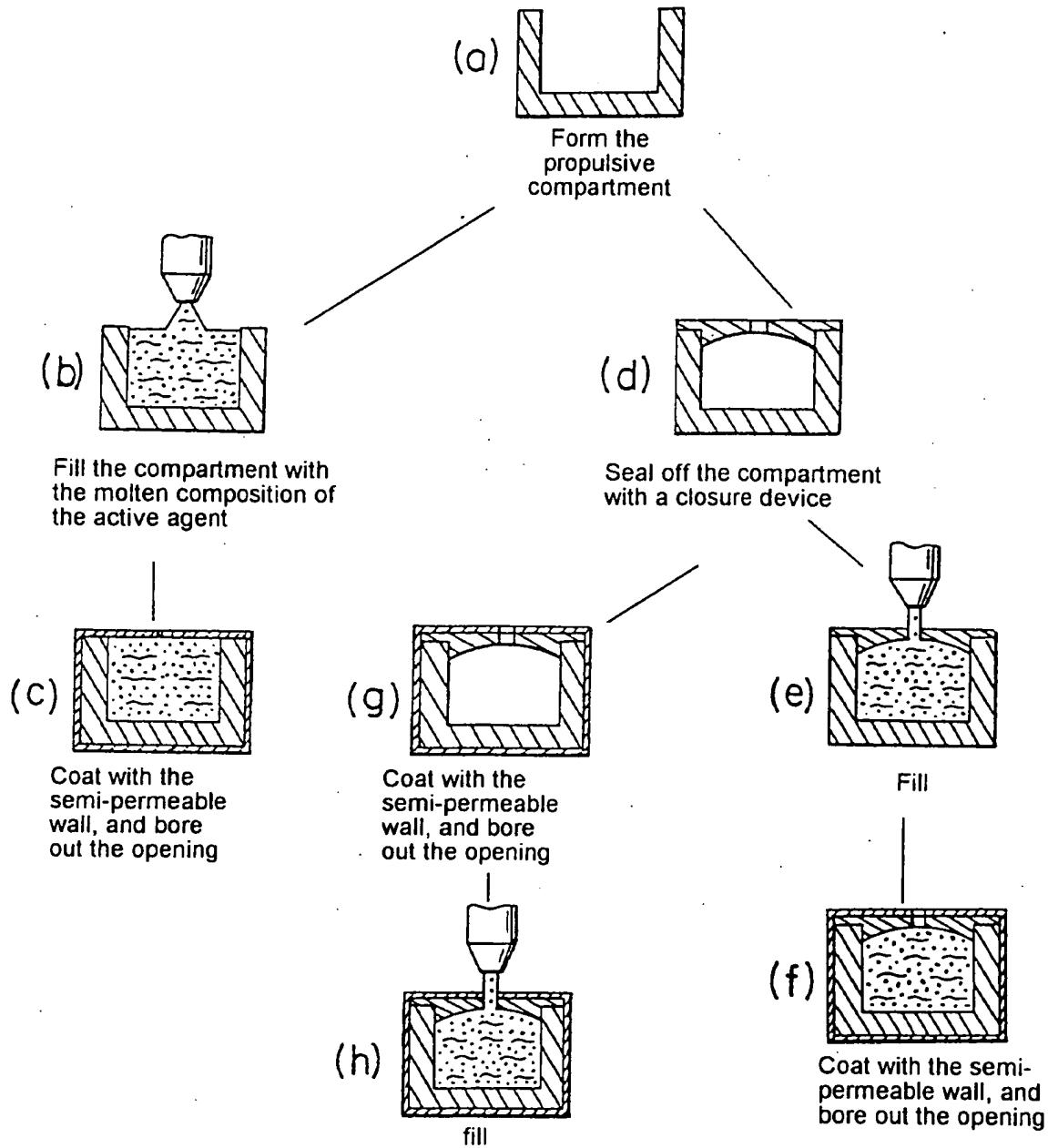


FIG. 8



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FIG.10



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Key to Figure 11 Graphs

- 1 = Osmotic pump that releases Witepsol H-15 as a result of propulsion and melting
- 2 = average  $\pm$  standard deviation
- 3 = position: vertically
- 4 = position: horizontally
- 5 = speed of release of Witepsol, mg/hour
- 6 = dwell time (days)
- 7 = total quantity of Witepsol released (%)

FIG.11

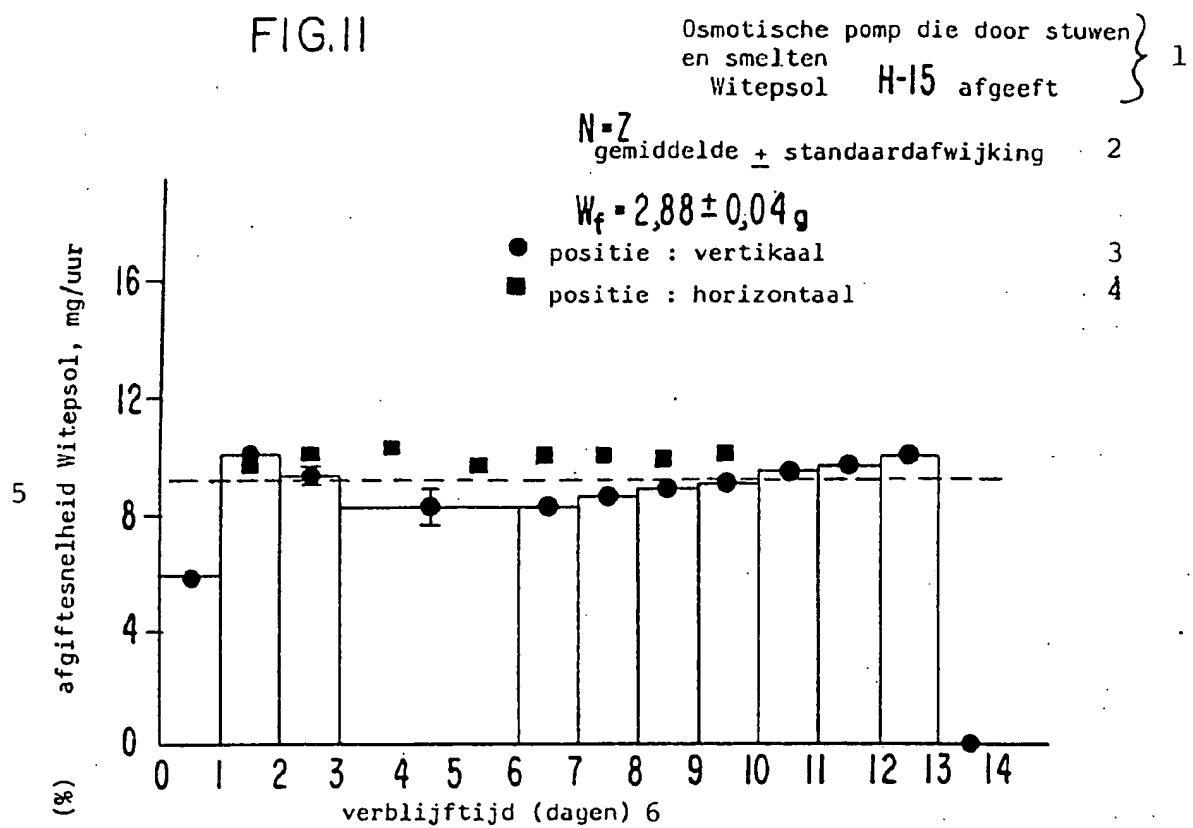


FIG.12

